Background on cholera and CVD 103-HgR

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Advisory Committee on Immunization Practices
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Background on cholera

- Toxin-mediated, acute watery diarrheal illness
- Caused by **toxigenic *Vibrio cholerae* O1 or O139**
  - Curved, motile, Gram-negative rods
- Can be severe and rapidly fatal without proper treatment
- Endemic in >50 countries
- Can cause large epidemics

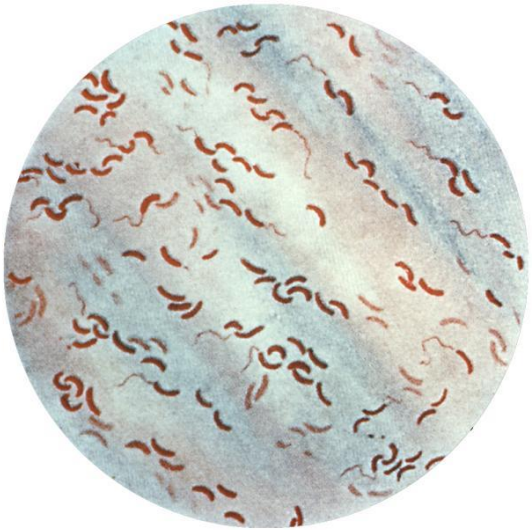


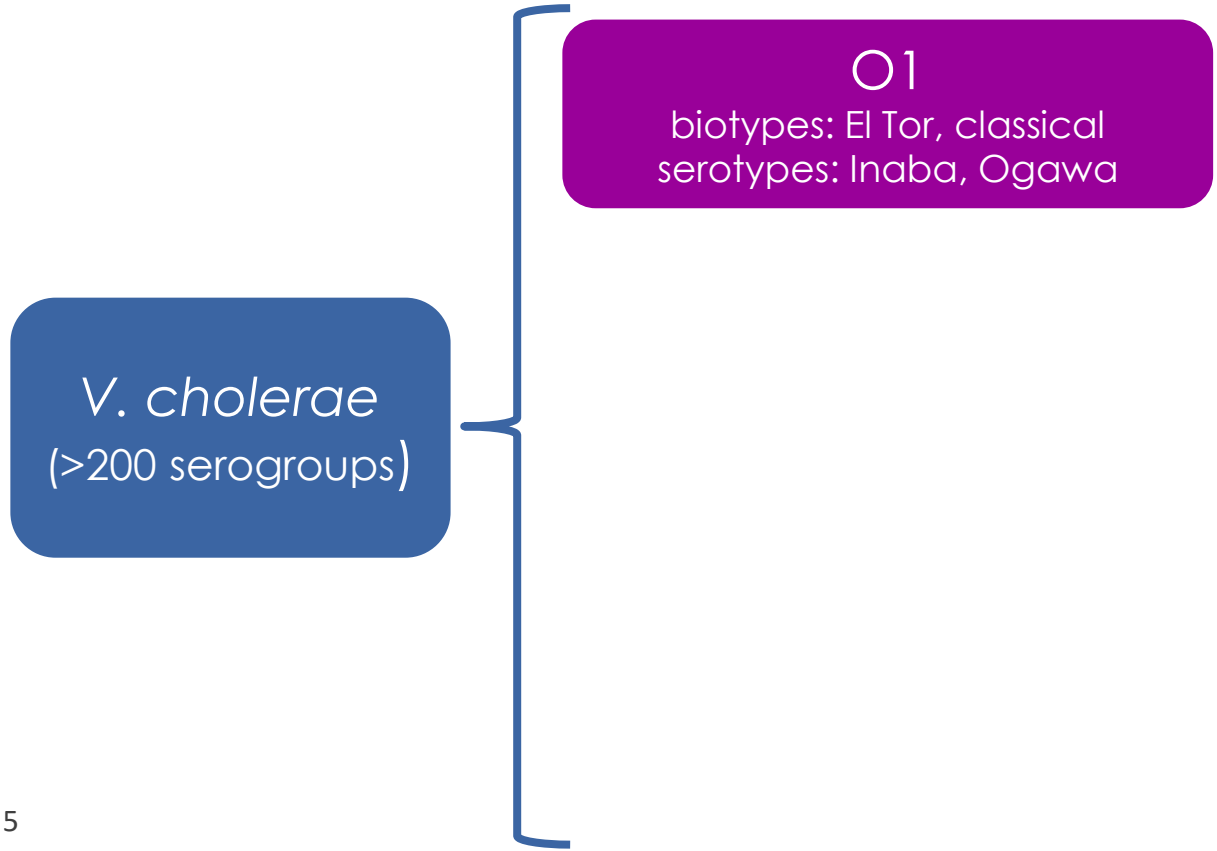
Photo: CDC Public Health Image Library

Microbiology and pathogenesis

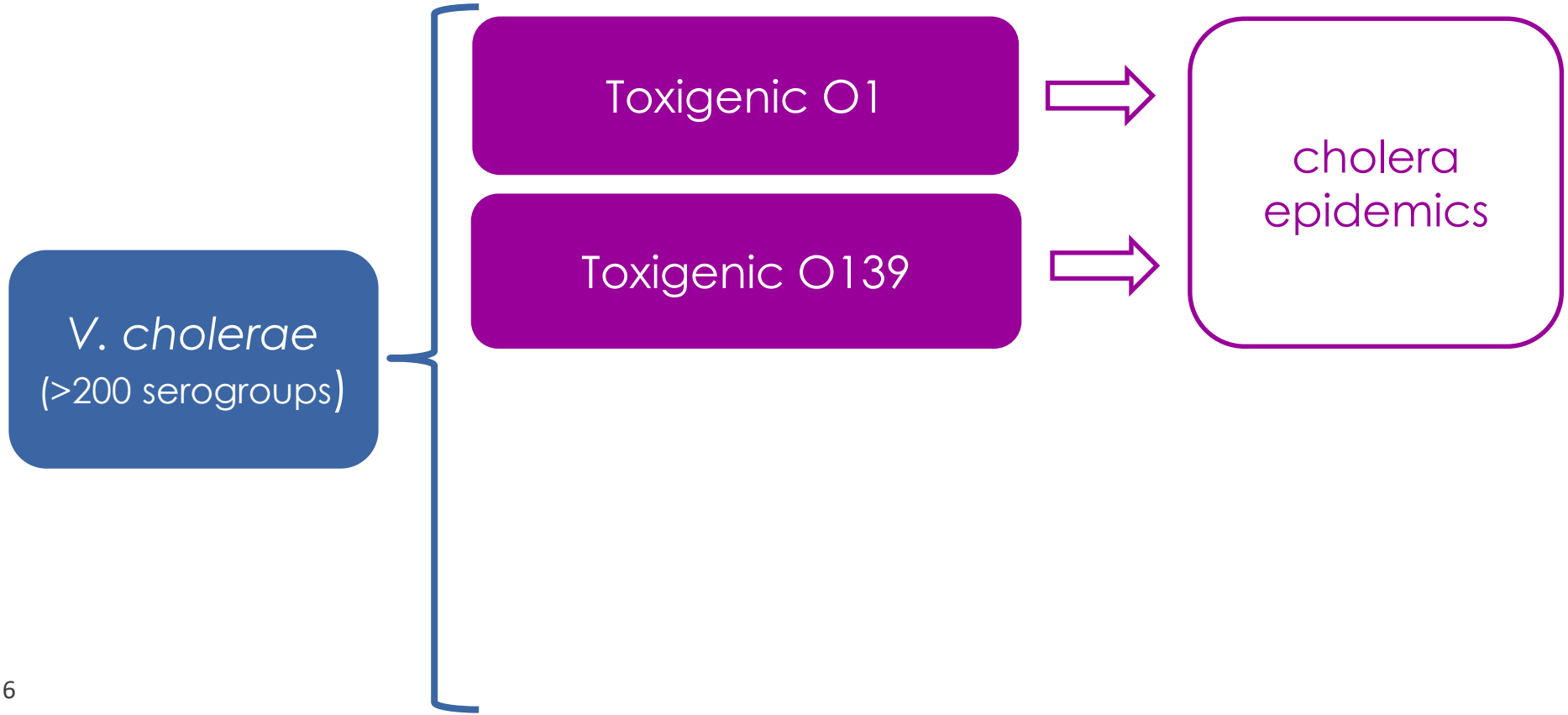
Vibrio cholerae is a diverse species with pathogenic and non-pathogenic variants

V. cholerae
(>200 serogroups)

Vibrio cholerae is a diverse species with pathogenic and non-pathogenic variants



Vibrio cholerae is a diverse species with pathogenic and non-pathogenic variants



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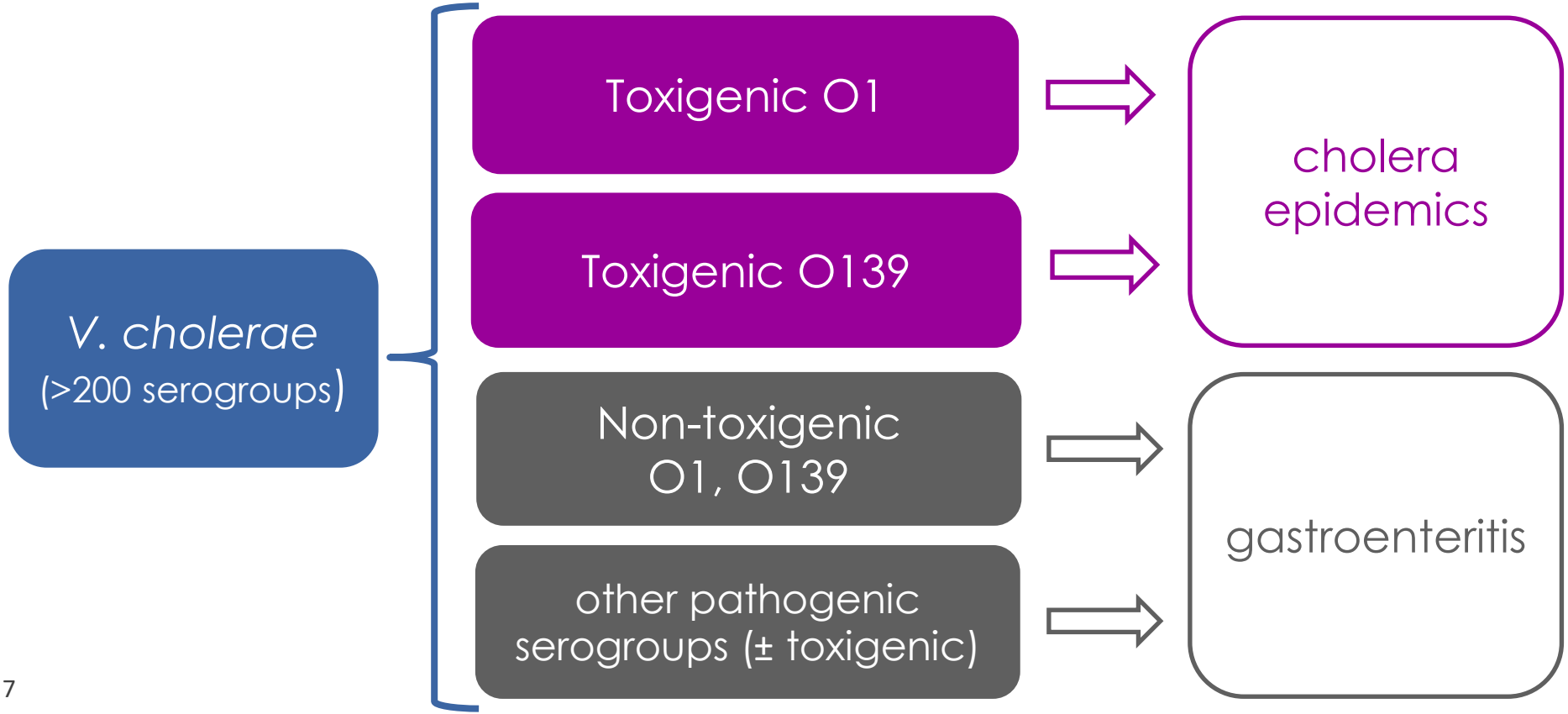


Cholera epidemics are associated with unsafe water and inadequate sanitation

- *V. cholerae* has an aquatic reservoir
- Human infection
  - ingestion of contaminated water or food
  - direct fecal-oral transmission
  - secondary cases rare if sanitation adequate
  - incubation period: hours to 5 days

Photo: Public Health Image Library, ID: 19647

Cholera is a toxin-mediated disease

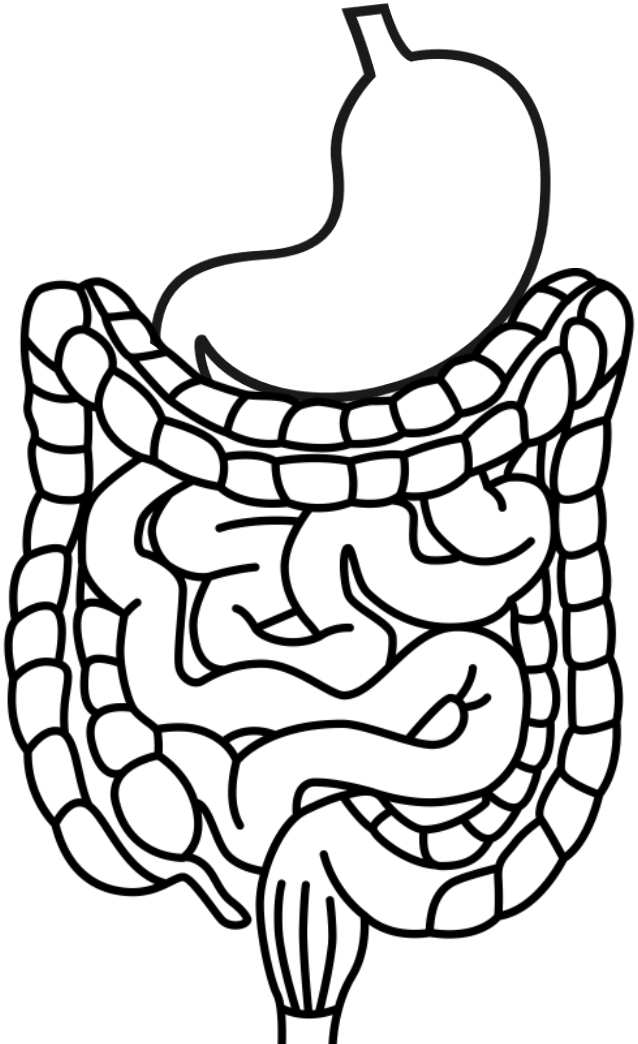
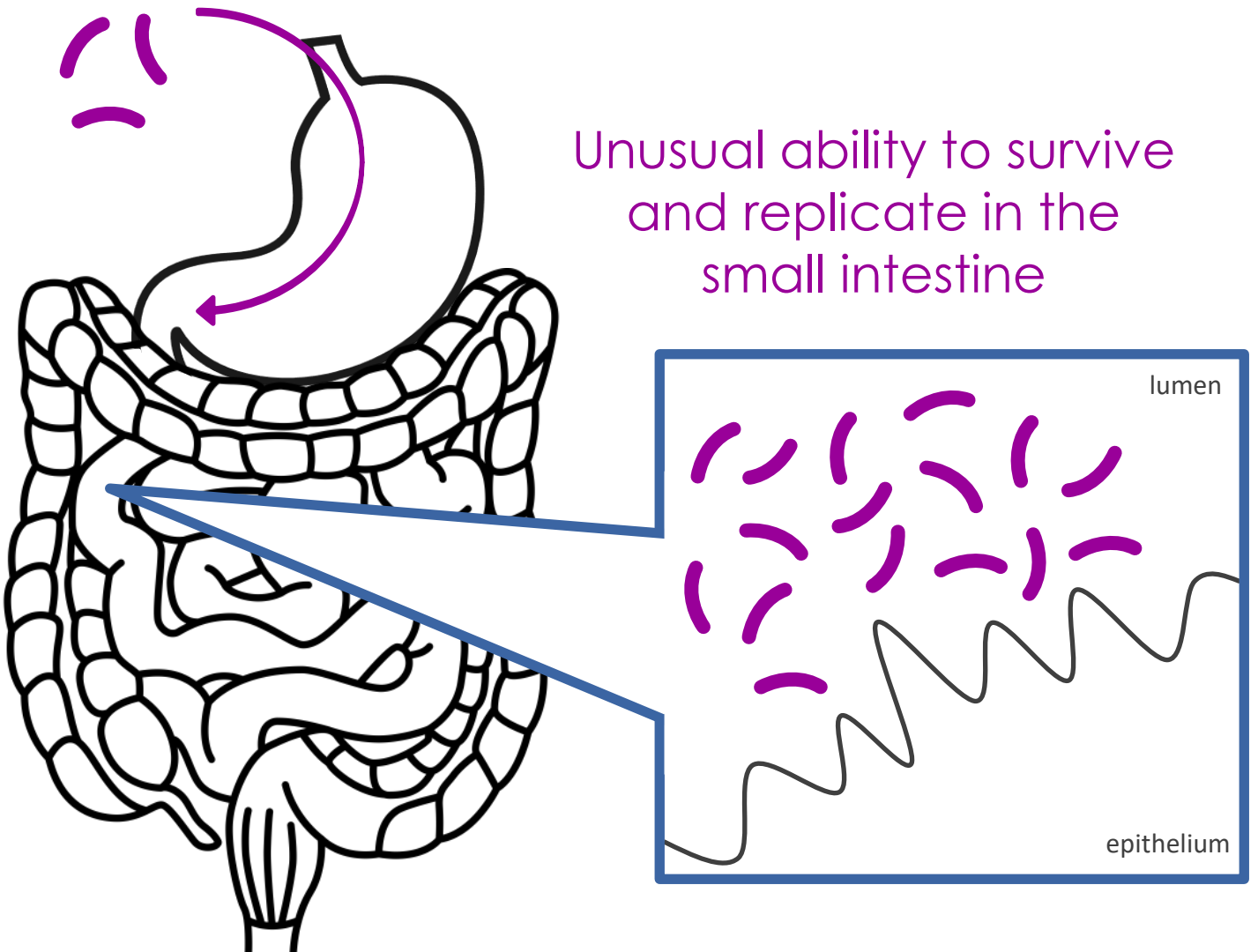


Image credits:
“Stomach” icon by Hermine Blanquart from the nounproject.com
“Intestines” icon by Tom Fricker from the nounproject.com

Cholera is a toxin-mediated disease



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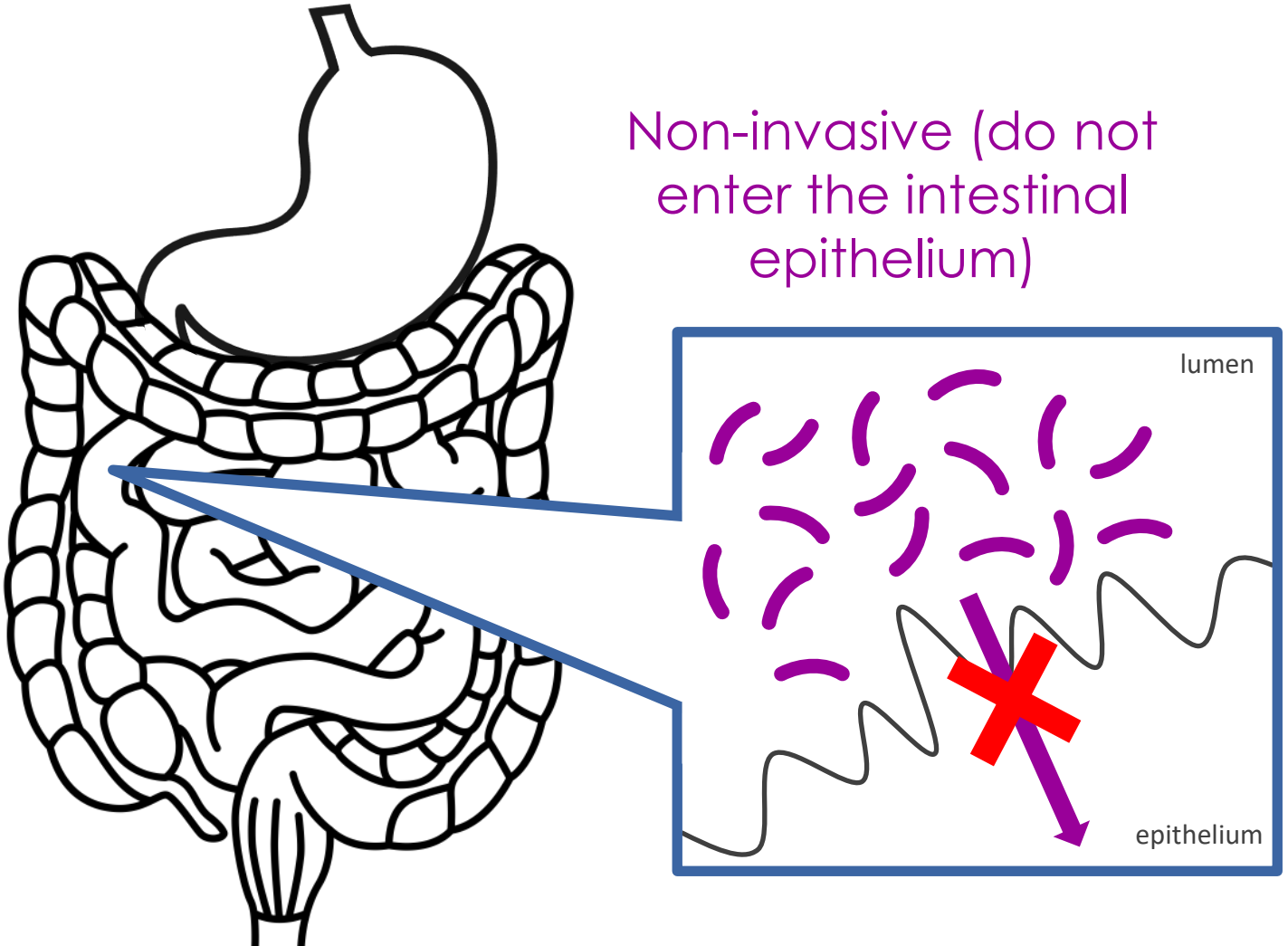

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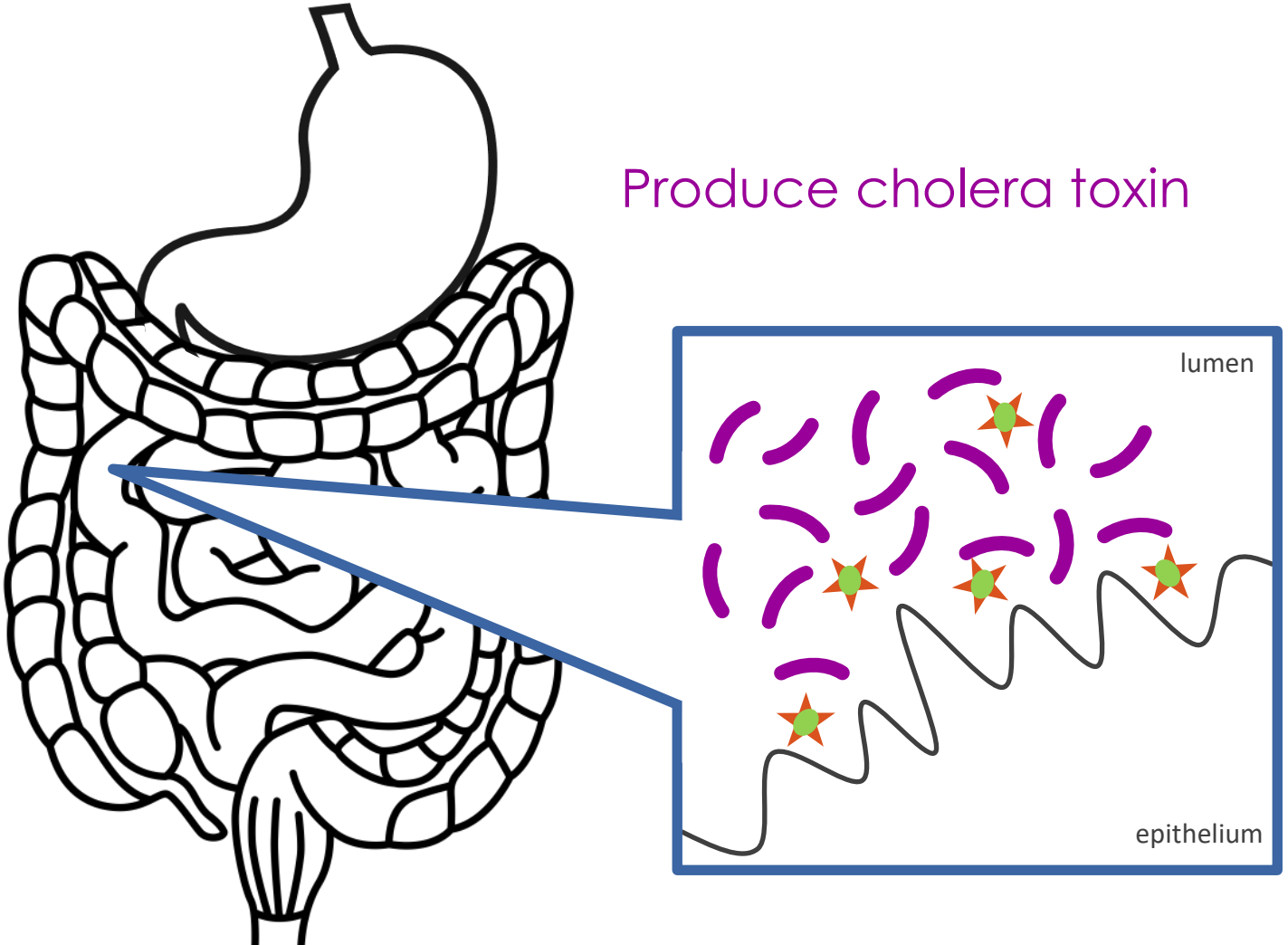
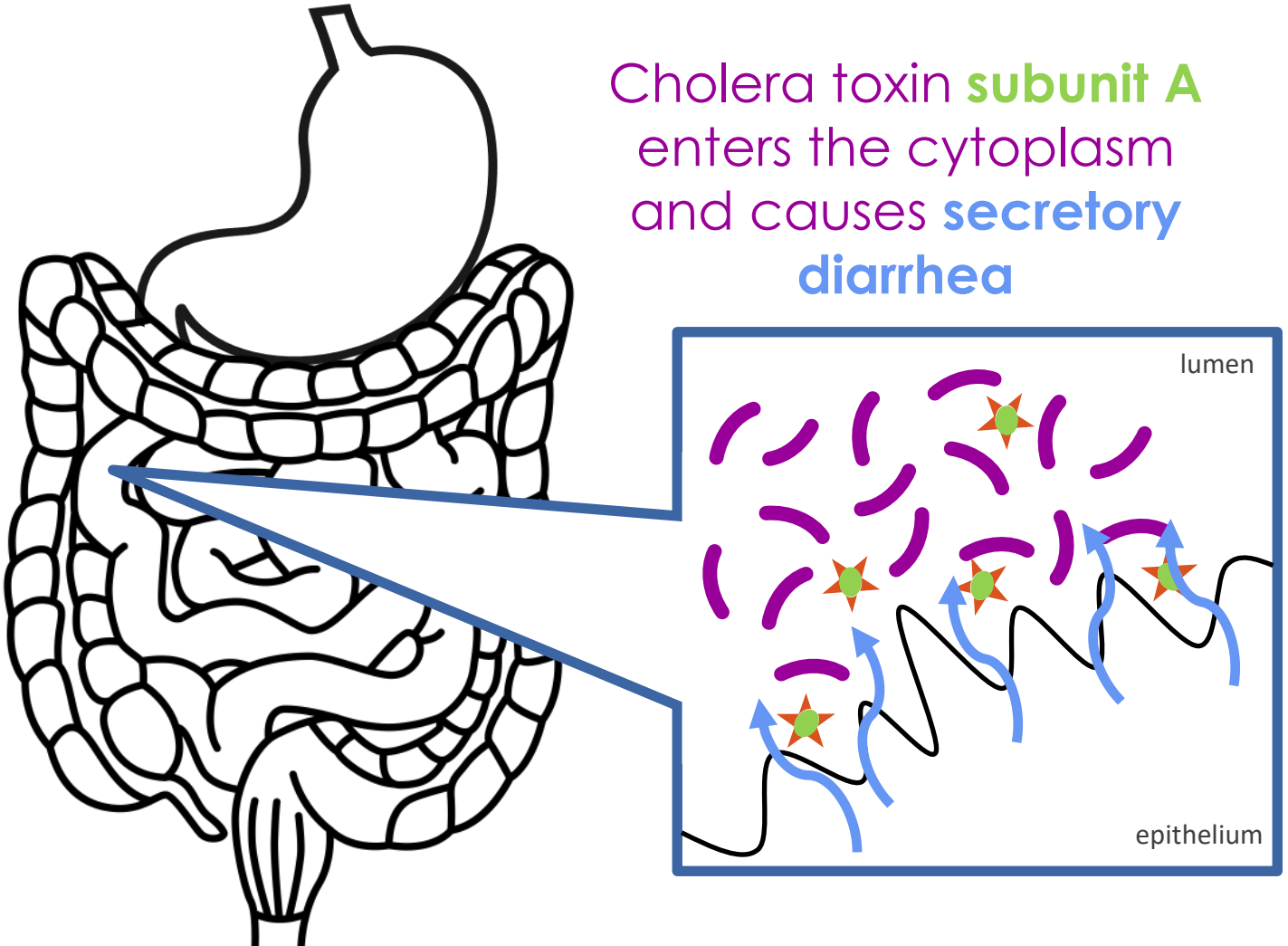


Cholera is a toxin-mediated disease

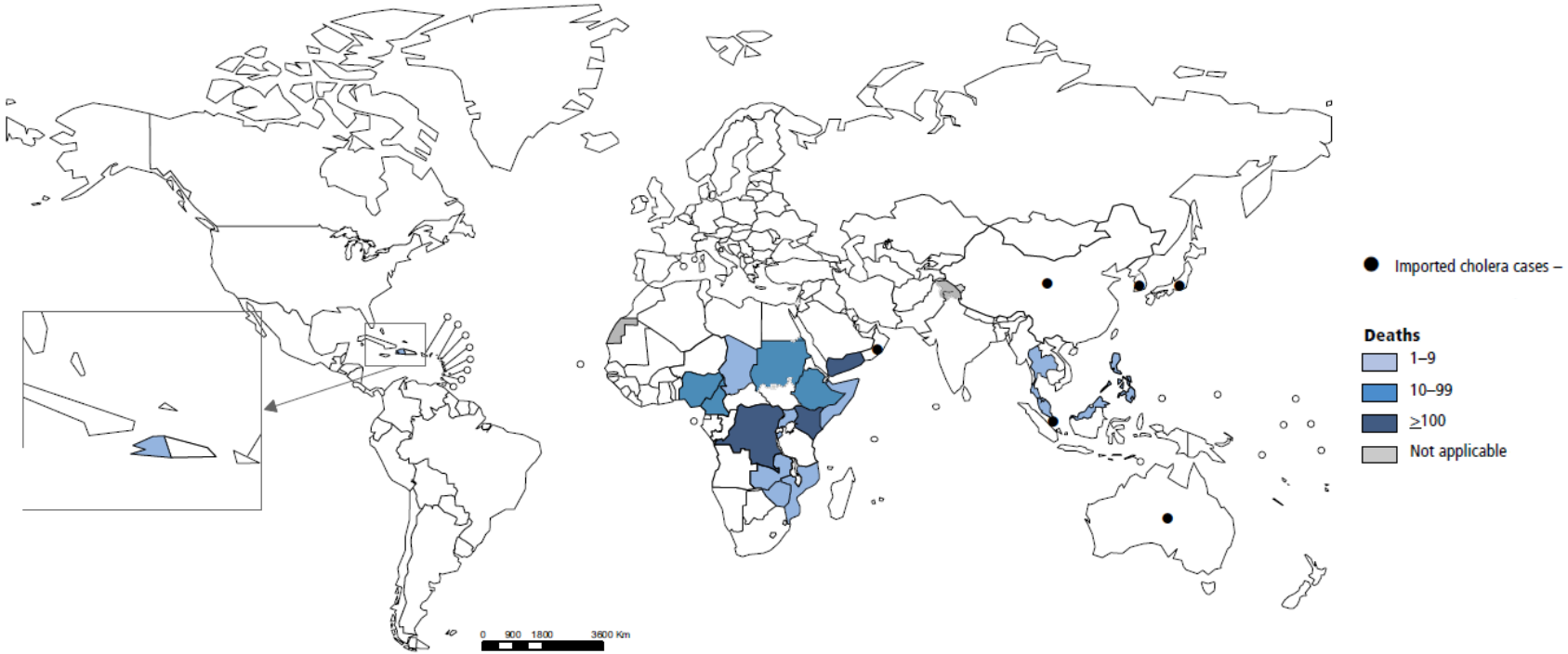


Epidemiology

Cholera can cause explosive epidemics

- Seven pandemics have been reported since 1817
- The **current global pandemic (El Tor O1)** began in 1961
- Serogroup O139 first emerged in 1992, in Asia
  - first non-O1 cause of epidemic cholera
  - now causes a small portion of cases

Asia and sub-Saharan Africa have the highest burden of cholera deaths

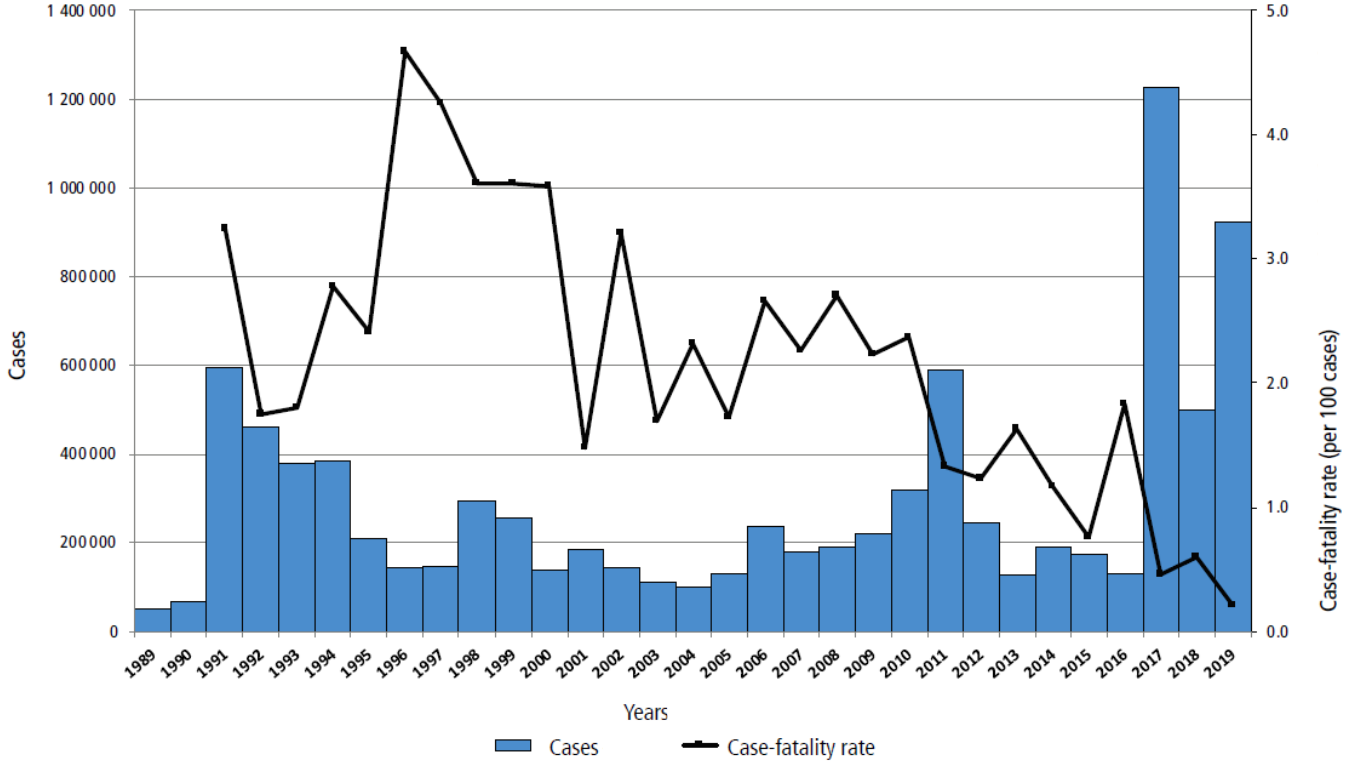


Countries reporting cholera deaths and imported cases to the World Health Organization (WHO), 2019

Source: WHO Weekly Epidemiological Record. 11 Sept 2020.

Cholera cases reported to WHO increased during 2017–2019

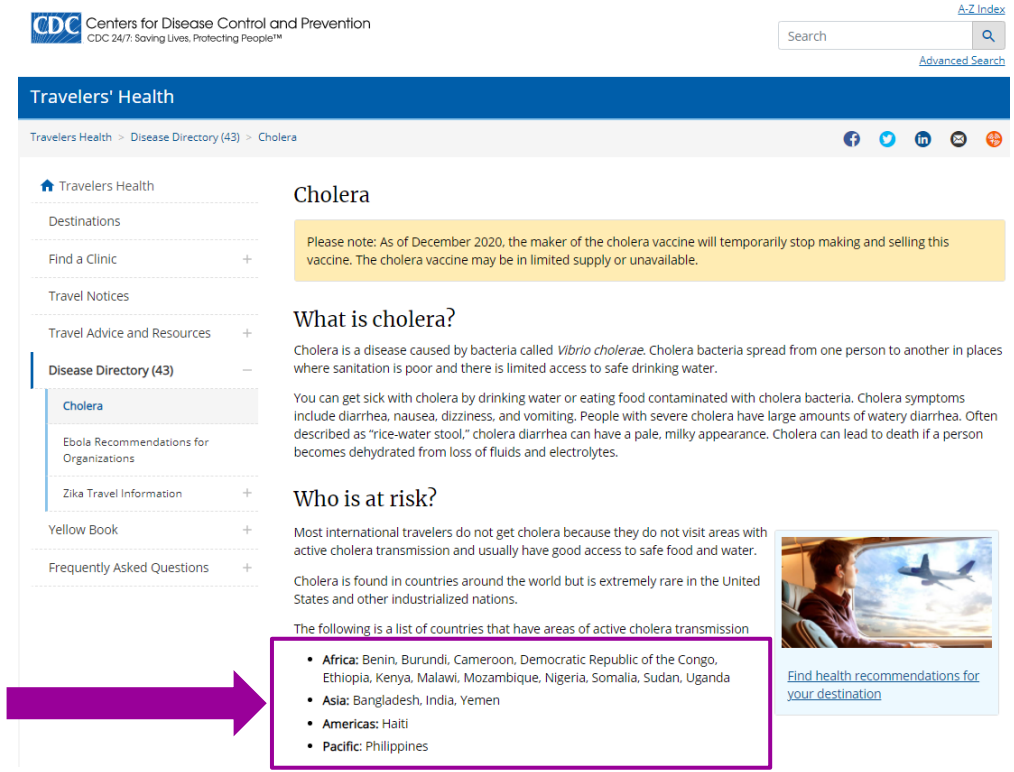
Annual cholera cases and mortality reported by year –WHO, 1989–2019



Source: WHO Weekly Epidemiological Record. 11 Sept 2020.

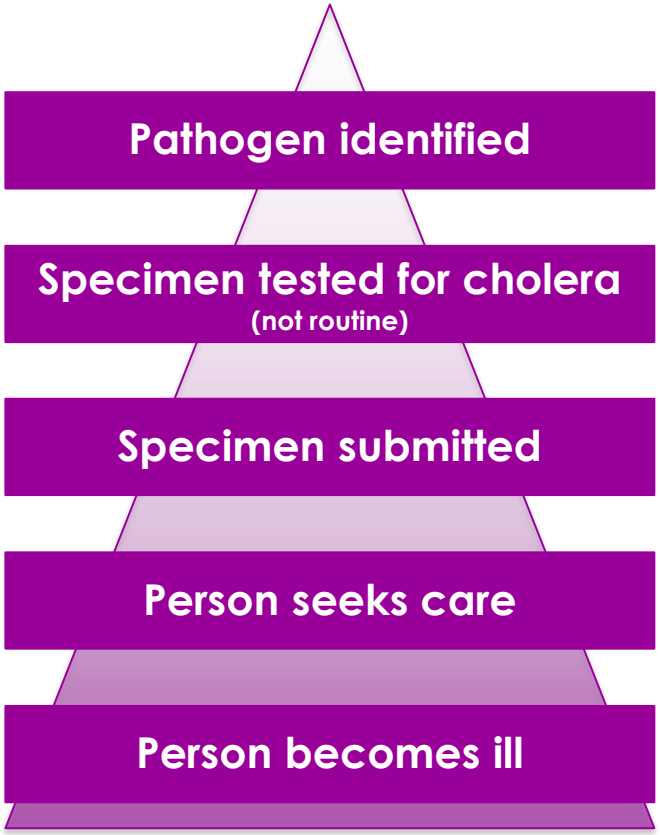
Cholera in the United States and other high-income countries is primarily travel-associated

- Most international travelers from the United States **do not get cholera**
  - Do not visit areas with active cholera transmission
  - Have good access to safe food and water
- CDC monitors areas with active cholera transmission



https://wwwnc.cdc.gov/travel/diseases/cholera#areas

Like most infections, cholera is underreported in the United States

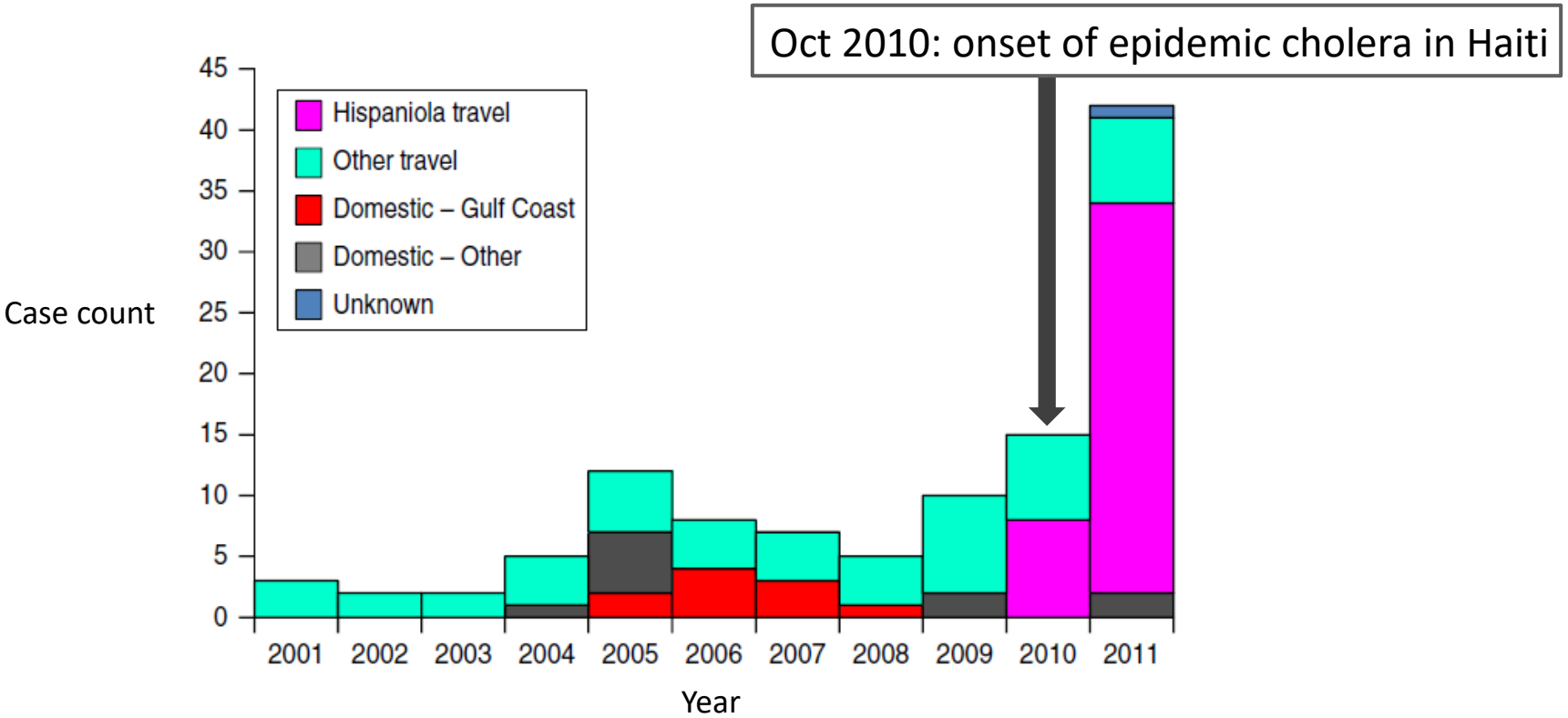


Cholera in the United States, 2001–2011

- 111 cholera cases over 11-year period
- Age
  - 1–85 years (median 44 years)
  - 15 (14%) 2–19 years old
- 108 diagnosed by stool culture; 107 were *V. cholerae* O1
- No deaths

Loharikar A *et al*. Cholera in the United States, 2001-2011: a reflection of patterns of global epidemiology and travel. *Epidemiol Infect*. 2015 Mar;143(4):695-703.

90 (81%) cases associated with international travel, 2001–2011



Loharikar A *et al*. Cholera in the United States, 2001-2011: a reflection of patterns of global epidemiology and travel. *Epidemiol Infect*. 2015 Mar;143(4):695-703.

Cholera in the United States, 2012–2018

- 64 patients with cholera reported
- Age
  - 11 months–87 years (median 51 years)
  - 5 (8%) 2–17 years old
- All *V. cholerae* O1
- 2 deaths (adults)

Cholera in the United States, 2012–2018

Age group (years)	Travel-associated*	Not travel-associated	Total
<2	2	0	2
2–5	2	0	2
6–17	3	0	3
≥18	49	8	57
Total	56	8	64

*International travel in the 7 days before illness began

56 (88%) cases were travel-associated

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5 (8%) cases in children and adolescents 2–17 years old

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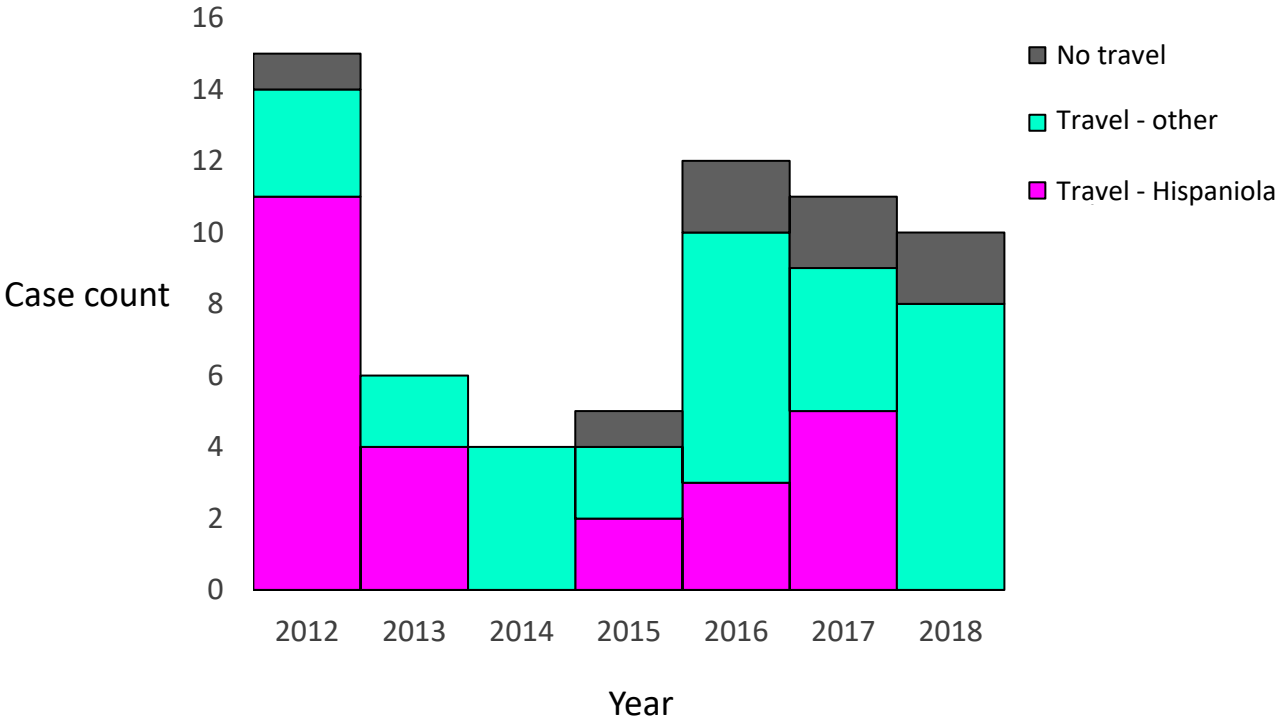
Annual case counts 15 or fewer during 2012–2018



Clinical manifestations and diagnosis

Clinical manifestations of cholera infection vary

Asymptomatic
~75%

Cholera gravis
~10%

Risk factors:
- High dose exposure
- Low gastric acidity
- Blood group O

Cholera gravis is rapidly fatal if untreated

- Profuse watery diarrhea
- “Rice-water stools” flecked with mucus and epithelial cells
- Vomiting
- Leg cramps
- Severe dehydration
  - loss of skin turgor
  - hypotension
  - weak pulse
  - altered mental status

A definitive diagnosis of cholera is based on culture of stool or rectal swab

- Transport media and selective culture media needed
- Other stool tests
  - Rapid antigen
  - Darkfield microscopy
  - Molecular assays

- Acute/convalescent serology sometimes used

Image: iStock by Getty images, ID: 638143058

Fluid management is the primary focus of cholera treatment

- Patients with cholera gravis may require up to 350 mL/kg of fluids within the first 24 hours of illness
- Moderately to severely ill patients should receive antibiotic therapy

Photo: iStock by Getty images, ID: 817180340

Immune response and vaccines

Immune response to cholera is serogroup-specific (O1 or O139)

- El Tor O1 and O139
  - genomes are very similar
  - identical cholera toxin genes
- Immune responses targeting cholera toxin common after cholera; do not mediate long-term protection
- Vibriocidal antibodies are best marker for protection against *V. cholerae* infection
  - Every two-fold increase associated with ~40% reduction in risk of cholera*
- Lipopolysaccharide-specific memory B cells may play role in mediating long-term protection**

*Mosley et al. Bull World Health Organ 1969; 40: 187–97.
**Patel et al. Clin Vaccine Immunol 10: 842–848; 2012

CVD 103-HgR was derived from wild-type *V. cholerae* O1

- Single-dose, live, attenuated oral vaccine
  - Inaba serotype, classic biotype
  - Cross-protective against other O1 serotypes and biotypes
  - 94% of gene encoding enterotoxin subunit A deleted
  - Expression of non-toxic B subunit left intact
  - Contains a marker to differentiate from wild-type *Vibrio*
- Lyophilized (freeze-dried powder)
- Reconstituted with a buffer solution to neutralize stomach acid

Commercial formulations of CVD 103-HgR

- Orochol, Mutacol (Berna)
  - $5x10^8$ colony-forming unit (CFU) dose
  - Licensed in non-US countries in the 1990s
  - Production discontinued in 2004

Commercial formulations of CVD 103-HgR

- Vaxchora (Emergent BioSolutions)
  - Dose range: $4x10^8$–$2x10^9$ CFU
  - Volume with buffer
    - 100 ml if ≥6 years
    - 50 ml if 2–5 years
  - Licensed by FDA
    - Adults 18 – 64 years (June 2016)
    - Children 2–17 years (December 2020)

Current ACIP recommendations for lyophilized CVD 103-HgR

Morbidity and Mortality Weekly Report (*MMWR*)

CDC

Recommendations of the Advisory Committee on Immunization Practices for Use of Cholera Vaccine

Weekly / May 12, 2017 / 66(18);482–485

Karen K. Wong, MD[1]; Erin Burdette, MPH[1]; Barbara E. Mahon, MD[1]; Eric D. Mintz, MD[1]; Edward T. Ryan, MD[2]; Arthur L. Reingold, MD[3] (View author affiliations)

Work group findings — efficacy & immunogenicity

- Efficacy against severe diarrhea (fecal output >3L/24 hours) after oral toxigenic V. cholerae O1 challenge*
  - Current formulation: estimated to be 90% at 10 days, 80% at 3 months
  - Similar efficacy in studies of the previous formulation

- Vibriocidal antibody response
  - Both formulations of the vaccine effectively induce these

*GRADE evidence type 1

Work group findings — adverse events

- Adverse events**
  - No vaccine-related serious adverse events for either formulation
  - Current formulation: slightly higher prevalence of diarrhea (mostly mild) among vaccine vs. placebo recipients (3.8% vs. 1.6%)
  - No other differences between vaccinated and unvaccinated groups

**GRADE evidence type 3

ACIP currently recommends CVD 103-HgR for adult travelers (18–64 years old) from the United States to an area of active cholera transmission.

ACIP currently recommends CVD 103-HgR for adult travelers (18–64 years old) from the United States to an area of active cholera transmission.

Policy topic under consideration:
Should ACIP cholera vaccine recommendations be expanded to include children and adolescents 2–17 years old?

Recently published pediatric studies

Am. J. Trop. Med. Hyg., 102(1), 2020, pp. 48–57
doi:10.4269/ajtmh.19-0241

Safety and Immunogenicity of Live Oral Cholera Vaccine CVD 103-HgR in Children and Adolescents Aged 6–17 Years

James M. McCarty,[1]* Emma C. Gierman,[2] Lisa Bedell,[2] Michael D. Lock,[2] and Sean Bennett[2]
[1]*Stanford University School of Medicine, Stanford, California;* [2]*PaxVax, Inc., Redwood City, California*

Am. J. Trop. Med. Hyg., 00(0), 2020, pp. 1–5
doi:10.4269/ajtmh.20-0917

Safety and Immunogenicity of Live Oral Cholera Vaccine CVD 103-HgR in Children Aged 2–5 Years in the United States

James M. McCarty,[1]* David Cassie,[2] Lisa Bedell,[2] Michael D. Lock,[2] and Sean Bennett[2]
[1]*Stanford University School of Medicine, Stanford, California;* [2]*Emergent Travel Health, Inc., Redwood City, California*

Studies of prior formulation of CVD 103-HgR among children

Safety and immunogenicity of single-dose live oral cholera vaccine CVD 103-HgR in 5–9-year-old Indonesian children

SUHARYONO CYRUS SIMANJUNTAK NANCY WITHAM
NARAIN PUNJABI D. GRAY HEPPNER GENEVIEVE LOSONSKY
HARDJINING TOTOSUDIRJO ATTI R. RIFAI JOHN CLEMENS
YU LEUNG LIM DONALD BURR STEVEN S. WASSERMAN
JAMES KAPER KURT SORENSON STANLEY CRYZ
MYRON M. LEVINE

Lancet 1992; **340**: 689–94.

Bol Med Hosp Infant Mex
Volumen 53-Número 5
Mayo, 1996

Artículos

Tolerancia, inmunogenicidad, excreción y transmisión de la vacuna anti-cólera oral viva-atenuada, CVD 103-HgR. Estudio pareado doble ciego en niños chilenos de 24 a 59 meses

R. Lagos[1], G. Losonsky[2], P. Abrego[1], O. San Martín[1], V. Prado[3], S. Wasserman[2], MM. Levine[2]

[1]Servicio de Salud Metropolitano Norte, Centro para Vacunas en Desarrollo-Chile; [2]Departamento de Microbiología, Facultad de Medicina, Campus Oriente, Universidad de Chile, Santiago, Chile; [3]Center for Vaccine Development, University of Maryland, School of Medicine, Maryland, Baltimore, U.S.A.

Safety, Immunogenicity, and Transmissibility of Single-Dose Live Oral Cholera Vaccine Strain CVD 103-HgR in 24- to 59-Month-Old Indonesian Children

Cyrus H. Simanjuntak, Peter O'Hanley, Narain H. Punjabi, Fernando Noriega, Gary Pazzaglia, Patricia Dykstra, Bradford Kay, Suharyono, Aswitha Budiarso, Atti R. Rifai, Steven S. Wasserman, Genevieve Losonsky, James Kaper, Stanley Cryz, and Myron M. Levine

National Institute of Health Research and Development, US Naval Medical Research Unit No. 2, and Department of Pediatrics, University of Indonesia, Jakarta, and Infectious Diseases Hospital, North Jakarta, Indonesia; VA Hospital, Palo Alto, and Departments of Medicine and Microbiology and Immunology, Stanford University School of Medicine, Stanford, California; Center for Vaccine Development, University of Maryland School of Medicine, Baltimore; and Swiss Serum and Vaccine Institute, Berne, Switzerland

The Journal of Infectious Diseases 1993;168:1169–76

0022–1899/93/6805–0012$01.00

ELSEVIER

Vaccine 18 (2000) 2399–2410

Vaccine

www.elsevier.com/locate/vaccine

Efficacy trial of single-dose live oral cholera vaccine CVD 103-HgR in North Jakarta, Indonesia, a cholera-endemic area

Emily Richie[a,b], Narain H. Punjabi[a], Yuwono Sidharta[c], Kenny Peetosutan[c], Melanie Sukandar[a], Steven S. Wasserman[d], Murad Lesmana[b], Ferry Wangsasaputra[a], Sri Pandam[b], Myron M. Levine[d,*], Peter O'Hanley[a,e], Stanley J. Cryz[f], Cyrus H. Simanjuntak[c]

INFECTION AND IMMUNITY, Feb. 1995, p. 707–709
0019-9567/95/$04.00+0

Vol. 63, No. 2

Attenuated Live Cholera Vaccine Strain CVD 103-HgR Elicits Significantly Higher Serum Vibriocidal Antibody Titers in Persons of Blood Group O

ROSANNA LAGOS,[1,2,3] ALFREDO AVENDAÑO,[2] VALERIA PRADO,[4] ISIDORO HORWITZ,[2] STEVEN WASSERMAN,[3] GENEVIEVE LOSONSKY,[3] STANLEY CRYZ, JR.,[5] JAMES B. KAPER,[3] AND MYRON M. LEVINE[1,3]*

Adverse events after oral vaccination against cholera with CVD103-HgR

Gerhard Wiedermann[1], Herwig Kollaritsch[1], Eva Jeschko[1], Michael Kundi[2], Christian Herzog[3], and Bernhard Wegmüller[3]

[1] Institute for Specific Prophylaxis and Tropical Medicine, and [2] Institute for Environmental Hygiene, University of Vienna, Austria
[3] Swiss Serum and Vaccine Institute (SSVI), Berne, Switzerland

Studies of prior formulation of CVD 103-HgR among children

- **5x10^8 CFU dose** was much less immunogenic among children in Indonesia than among adults in industrialized countries*
- **5x10^9 CFU dose**
  - 51–81% vibriocidal seroconversion
  - Shedding of vaccine strain was infrequent
  - Vaccine generally well tolerated; fever more common among vaccine recipients in one study (18 vs. 9%)**
  - Single-dose did not confer long-term protection***
  - **Dose was higher than Vaxchora (4x10^8–2x10^9 CFU)**

*Suharyono et al. *Lancet.* 1992;340:689-94
**Simanjuntak et al. *JID*. 1993;168:1169-76
***Richie et al. *Vaccine*. 2000; 18; 2399-2410

Summary

- Cholera
  - Toxin-mediated, acute watery diarrheal illness that can be severe and rapidly fatal without proper treatment
  - Endemic in >50 countries and can cause explosive epidemics
  - Most US cases occur among travelers to cholera-endemic areas
  - Immune response is serogroup-specific (O1 or O139)
- CVD 103-HgR
  - Single-dose, live, attenuated serogroup O1 oral vaccine
  - ACIP currently recommends for adult travelers (18–64 years old) from the United States to an area of active cholera transmission

Thank you!

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov